Urotensin-II and endothelin-I levels after contrast media administration in patients undergoing percutaneous coronary interventions


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Background: Contrast induced kidney injury is an acute renal dysfunction that is secondary to the administration of radio contrast media. The purpose of this study was to evaluate the levels of urotensin-II (UT-II) and endothelin-I (ET-I) after contrast media administration in patients undergoing percutaneous coronary interventions. Materials and Methods: In this prospective cohort study, we evaluated 78 patients with coronary artery disease who were scheduled for and ultimately underwent percutaneous coronary interventions. As a contrast material, nonionic contrast media was used in various amounts (70–480 mL). Blood and urine samples were obtained to measure UT-II, ET-I just before and at the twenty-fourth hour of percutaneous coronary interventions. Results: Compared to baseline, twenty-fourth hour creatinine levels were significantly increased (P < 0.001). The twenty-fourth hour serum and urine levels of both UT-II and ET-I were also significantly increased compared to baseline (P < 0.001 for all) and 24th hour serum and urine UT-II (r = 0.322, P = 0.006; r = 0.302, P = 0.007 respectively) and ET-I (r = 0.511, P < 0.001; r = 0.266, P = 0.019 respectively) levels were significantly correlated with the amount of contrast media. Conclusion: Our study indicates that; increased UT-II and ET-I levels seem to be a consequence of hazardous effects of contrast media on blood vessels and the kidney.

Key words: Acute kidney injury, contrast media, coronary angiography, endothelin-I, urotensin-II

INTRODUCTION

Renal hemodynamics changes due to the effects of contrast media (CM) depending on the action of many mediators, and the mediators are not still clearly known. Dopamine-I, adenosine, angiotensin II, nitric oxide, and endothelin are accused of the process.[1-8] It is known that urotensin-II (UT-II) and endothelin-I (ET-I) are highly expressed in the kidney, which may be the principal site of UT-II and ET-I synthesis in humans, and also expressed from all endothelial cells.[9-12] CM injection related endothelial damage based on histopathological endpoints; leads to apoptosis, cell death of endothelial and tubular cells and may be initiated by cell membrane damage.[13] Mechanical shear stress besides physicochemical properties such as osmolality or viscosity cause endothelial damage.[14]

A reduction in renal perfusion caused by a direct effect of CM on the kidney and toxic effects on the tubular cells are generally regarded as the main factors. However, the pathophysologic relevance of direct effects of CM on tubular cells is contentious.[15,16] Although based upon these relationships between CM, UT-II and ET-I mentioned above, no clinical research has been performed yet to investigate these mediators on kidney injury. By this way, we aimed in our study to investigate both the serum and urine levels of UT-II, ET-I after CM administration in patients undergoing percutaneous coronary intervention.

MATERIALS AND METHODS

Study design and patients

This prospective cohort study was conducted at the Harran University School of Medicine, Sanliurfa, Turkey. Prior to subject recruitment, the study protocol was reviewed and approved by the local ethics committee, in accordance with the ethical principles for human investigations (Ethical approval number: B.30-2-HRÜ.020.05.00.050.0 1.04-0101), as outlined by the Second Declaration of Helsinki and written informed consents were obtained from all the patients. From January-2011 to July-2011 consecutively 78 patients with coronary artery disease who were scheduled for and ultimately underwent PCI (according to prior coronary angiography results) and who had no exclusion criteria were recruited to the study.

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The exclusion criteria that would influence UT-II, ET-I and renal functions were as follows: intravascular administration of iodinated CM within 7 days before study entry or a history of serious reaction to intravascular iodinated CM; the administration of theophylline, N-acetylcysteine, or mannitol within 7 days before or after contrast administration; the initiation, discontinuation, or change in dose of any of the following angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker-within 72 h before study entry; initiation of nephrotoxic agents, or non-steroidal anti-inflammatory drugs within 72 h of study entry; acute coronary syndromes; any coexisting cardiac disease; any evidence of liver, kidney, or respiratory disease; diabetes mellitus; malignancy; any infectious, inflammatory, or infiltrative disorders; unregulated hypertension; reduced left ventricular ejection fraction, or any findings or history of congestive heart failure; pregnancy; lactation. Just before the PCI, blood and urine samples were obtained to measure baseline UT-II, ET-I.

As a contrast material, nonionic CM was used in various quantities (70-480 mL) depending on the clinical indications (Xenetix 300; Guerbet, Roissy, France, contains Iobitridol in 300 mg iodine/mL concentration). Adequate hydration was ensured before the procedure by advising all patients to drink at least 1500 mL of water during the preceding 24 h. In addition, just before the procedure, each patient was given 500 mL isotonic saline. Patients were also hydrated to ensure at least 2000 cc urine output after the procedure. Blood and urine samples were obtained again to measure UT-II, ET-I at 24 h.

Baseline definitions and measurements
Height and weight were measured according to standardized protocols. Body mass index was calculated as the weight in kilograms divided by the height in meters squared (kg/m²). Blood pressure was measured using an aneroid sphygmomanometer. The average of three BP levels were measured by new fluorescent enzyme immunoassay (EIA) kits (Phoenix Pharmaceuticals, Burlingame, CA, USA). For the UT-II immunoreactivity assay, the cross-reactivity with human UT-II was 100%. No cross-reactivity was found with human ET-I, angiotensin II, bradykinin, neurotensin or brain natriuretic peptide. For the ET-I immunoreactivity assay, cross-reactivity with human ET-I was 100%. No cross-reactivity was found with human angiotensin II and [Arg²]-Vasopressin. The intra- and inter-assay coefficients of variation for both UT-II and ET-I were <10%.

Other variables
Serum urea, creatinine, fasting blood glucose, aspartate aminotransferase, alanine aminotransferase, triglycerides, total cholesterol, high-density and low-density lipoprotein cholesterol levels were determined using the commercially-available assay kits (Abbott®, Abbott Park, North Chicago, Illinois, USA) with an auto-analyzer (Abbott®, Abbott Park, North Chicago, Illinois, USA).

Statistical analysis
All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov test was used to test the normality of data distribution. The data were expressed as arithmetic means and standard deviations. Paired T-Test and Wilcoxon signed-rank tests were used to analyze changes within each group. Pearson’s correlation analysis was used to examine the association of demographic and biochemical variables. A linear regression analysis was performed to identify the independent predictors of UT-II and ET-I levels. A two-sided P value < 0.05 was considered statistically significant.

RESULTS
Clinical, laboratory and demographic characteristics of all subjects were presented on Table 1. Compared to baseline, twenty-fourth hour creatinine levels were significantly increased (P < 0.001). The twenty-fourth hour serum and urine levels of both UT-II and ET-I were also significantly increased compared to baseline (P < 0.001 for all) [Table 2].

In bivariate analysis, twenty-fourth hour serum and urine UT-II (r = 0.322, P = 0.004; r = 0.302, P = 0.007 respectively), ET-I (r = 0.511, P < 0.001; r = 0.266, P = 0.019 respectively) levels were significantly correlated with the amount of CM [Table 3, Figure 1]. In a linear regression model with UT-II as a dependent variables, and the other continuous variables as an independent factors; no effect on UT-II levels were observed (r = 0.453, adjusted $r^2 = 0.205, P = 0.567$). In another model, in which ET-I level as a dependent variable the only CM was found to affect ET-I levels (r = 0.634, adjusted $r^2 = 0.232, P = 0.001$).
DISCUSSION

The present study yielded intriguing results, and the main findings were that; (i) twenty-fourth hour levels both in serum and urine samples of UT-II and ET-I were significantly increased compared to baseline, (ii) and were significantly correlated with the amount of CM.

The exact pathogenesis of contrast agent induced injury is still unclear, which is considered to arise from interactions of several major pathogenetic mechanisms. Researchers found evidence for direct renal tubular cell toxic effects of CM. The CM induces renal vasoconstriction and subsequently causes renal medullary ischemia leading to tubular injury or even necrosis and eventually reduces the glomerular filtration rate. This reduction may have direct cytotoxic effects due to high tissue osmolality on the renal tubules that undergo vacuolization and apoptosis and increase the local release of vasoconstrictive mediators such as ET-I, adenosine, free oxygen radicals, and calcium ions after CM administration.

Changes of UT-II levels in the plasma and urine in patients with renal dysfunction imply a role of UT-II in renal diseases. Plasma and urinary concentrations of UT-II are increased in essential hypertension; plasma UT-II is also increased in patients with renal dysfunction and in type II diabetics with renal nephropathy. Nothaker et al. suggested that the kidney was the principal site of UT-II synthesis in humans, while Matsushita et al. proposed that the human UT-II measured in urine was mainly derived from a renal source.

Several previous reports showed that ET-I has a pivotal role in the pathogenesis of acute renal failure of various etiologies, including ischemia, CM, glycerol injection, and obstruction. Namely, it has been reported that renal injury

![Figure 1](https://www.mui.ac.ir)
induces synthesis of endogenous ET-I, which then leads to continuation of its own production after the cessation of initial injury.[27] It is noteworthy that renal medullary ET-I synthesis is higher than any other body tissue and renal vasculature shows greater sensitivity to ET-I than other vascular beds in the systemic circulation.[10] An involvement of endothelin in contrast induced nephropathy appears likely due to the enhanced endothelin levels in plasma and urine, which is observed after radio contrast application.[13] In addition, the transcription and release of endothelin from endothelial cells is enhanced by CM. Moreover, in patients suffering of impaired renal function, the increase in endothelin after giving radio contrast is exaggerated.[15] Abassi ZA et al. reported that large amounts of ET are found in the urine compared with the small amounts present in blood and proposed that degradation of ET in the proximal tubule which filtered ET from plasma by neutral endopeptidases and that urinary ET is probably renal origin[28] would be the mechanisms for the inconsistency of serum and urine with regard to ET levels. Also Tsau YK et al. suggested that renal production, rather than clearance from the circulation by glomerular filtration, may be the source of urinary ET-I.[29]

However, it is important to note that only a very limited number of studies have been performed to investigate both UT-II and ET-I levels. Chai SB et al. suggested that increased plasma levels of UT-II and ET-I due to the injured endothelium following percutaneous transluminal coronary angioplasty.[11] In this study, baseline and twenty-fourth hour of both UT-II and ET-I levels were found to be increased compared to healthy subjects. At third day ET-I levels were found to be increased than baseline, however ET-I levels were similar with baseline levels. The UT-II and ET-I levels were found to be decreased at seventh day after the percutaneous transluminal coronary angioplasty. However, the authors have not declared the CM amount and have not correlated the amount of CM with UT-II and ET-I levels.[11] Hirose T. et al. investigated possible changes of the UT-II expression in cardiovascular tissues with hypertension; they examined and compared the gene expression of UT-II with ET-I, in heart, aorta and kidney of hypertensive rats in comparison with control rats and expression of UT-II gene was significantly increased in the aorta, similarly to those in the kidney in contrast to significantly decreased expression of ET-I gene.[29] In our study, we found an increased UT-II and ET-I levels both in the serum and urine after twenty-fourth hour of CM administration compared to baseline. These findings raised the possibility that, CM injures both endothelial and tubular cells, and causes increased expressions of these levels.

Certain limitations of the present study should be considered. Firstly, it is a single center study and the sample size was relatively small. Secondly, more detailed information would be gained by assessing UT-II and ET-I levels in consecutive days the investigation would perhaps
provide deeper insight to the pathogenesis of the kidney injury and might add to the value of our manuscript.

CONCLUSION

Both UT-II and ET-I were found to be increased after the CM administration -which would be a consequence of the hazardous effects of CM on endothelial and tubular cells- and increased UT-II and ET-I might be the biochemical markers of renal injury after CM. Future large-scale prospective cohort studies are needed to confirm/exclude the findings of the present study and to elucidate the pathophysiological mechanisms of increased UT-II and ET-I levels after CM.

REFERENCES


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